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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,749	01/14/2002	Michael Vajdy	16464.003	5494

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EXAMINER	
BROWN, TIMOTHY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,749	VAJDY ET AL.	
	Examiner	Art Unit	
	Timothy M. Brown	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *Claims 1-5, 8-21 and 29-34* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *Claims 1-5, 8-21 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/12/04; 6/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication mailed August 31, 2005. Claims 1-5, 8-21 and 29-34 are under examination. Claims 6, 7 and 22-28 are withdrawn.

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2005 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The scope of claim 15 is indefinite in that it recites "wherein said alphavirus vector comprises elements from two or more."

Claim 15 is indefinite in the recitation of "elements." This language is indefinite because it fails to define the structure of the alphavirus vector with particularity. One skilled in the art would not understand what is encompassed by "elements" since it might

refer to structural proteins, a gene encoding an antigen or non-structural protein, or a functional genetic sequence such as an IRES or promoter. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-21 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Undue experimentation is defined by the following factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Here, Applicants' invention is drawn to a method of generating an immune response which comprises administering a gene delivery vehicle that encodes a modified antigen. Thus, the breadth of the claims provides that the encoded antigen can be altered by any means including the deletion, substitution or insertion of amino acids. The state of the art at the time this application was filed was such that modifying the amino acid

composition of any antigenic peptide was known to produce an unpredictable effect expression and antigenicity. This is supported by the observation that variations in HIV-1 epitopes can have a destructive effect on the MHC I- and the MHC II-mediated immune response (J. Exp. Med. (1998) 188, 10, 1785-1793). Thus, one skilled in the art would have to look to the specification for directions on how to make and use Applicants' modified antigen. The specification, however, does not detail a single modified antigen that generates an immune response when administered mucosally through a gene delivery vehicle. Rather, the content of the specification relates to Sinbis replicons that encode an unmodified gag protein. The specification does not detail or teach altering the gag protein sequence to produce an antigenic peptide. Thus, the specification fails to overcome the unpredicitable effects of antigen modification discussed above. Based on this lack of instruction, one skilled in the art would have to invest undue experimentation in order to practice the claimed invention.

Claims 1-5, 8-21 and 29-34 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In this case, Applicants' claims are drawn to a method of generating an immune response which comprises administering a gene delivery vehicle that encodes a modified antigen. The specification, however, fails to provide adequate written description for the modified antigen. The specification teaches an antigenic replicon particle comprising a Sinbis virus/gag protein construct. The specification, however, does not disclose any

modifications to the gag portion of the construct. The specification similarly fails to detail the regions and/or amino acids that are critical to immunogenicity. Based on this lack of disclosure, one skilled in the art could not reasonably conclude that Applicants' were in possession of the modified antigen as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> *A person shall be entitled to a patent unless –*
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8-14, 16-21 and 29-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Malone et al. (U.S. Pat. No. 6,110,898) ("Malone").

Applicants' invention is drawn to a method of generating a cellular immune response comprising administering, to target cells in the mucosa of a subject, a polynucleotide that encodes an antigen, wherein the antigen-encoding polynucleotide is administered according to a multiple dose schedule. The invention provides that the antigen-encoding polynucleotide may be administered using a Sinbis virus vector, and that the antigen may comprise an HIV-1 polypeptide. The antigen-encoding polynucleotide may be administered to the vaginal, rectal or nasal mucosa where it may contact antigen-presenting dendritic cells. The invention

provides that a nucleotide encoding a Class I and/or a Class II MHC protein may be administered prior, or subsequent to, administering the antigen-encoding polynucleotide.

Malone anticipates the invention because it discloses a method of inducing a mucosal immune response wherein an antigenic polynucleotide is administered to the vaginal, nasal or rectal mucosal membranes of a subject according to a multiple dose schedule (abstract, lines 2-4; col. 14, lines 64-66; col. 15, lines 57-62; and col. 17, lines 14-17 and 61-63). Malone's antigenic polynucleotide may be derived from a sexually transmitted virus such as HIV-1 (col. 20, lines 7-10 and 23-25). Malone further provides that the polynucleotide is delivered by an alphaviral vector such as Sinbis or Semliki Forest virus (col. 11, lines 39-41). Malone's alphaviral vector comprises a replicon (col. 2, line 66-col. 3, line 1). Malone discloses introducing a nucleic acid that encodes a Class I and/or a Class II MHC protein (col. 4, lines 60-65).

Note that Malone inherently discloses presenting an antigenic polynucleotide to dendritic cells. This results because mucosal membranes are a natural environment for dendritic cells. Thus, by introducing an antigenic polynucleotide to a mucosal surface, Malone necessarily discloses presenting the antigenic polynucleotide to dendritic cells.

Note that Malone inherently teaches eliciting an HLA class I or HLA class II response. This results because Malone teaches administering the antigen-encoding polynucleotide to a human which would necessarily cause an HLA class I and HLA class II response.

Claims 1,.3, 5, 8-12, 18-20 and 31-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Belyakov et al. (Belyakov, I.M. "Induction of a Mucosal Cytotoxic T-Lymphocyte Response by Intrarectal Immunization with a Replication-Deficient

Recombinant Vaccinia Virus Expressing Human Immunodeficiency Virus 89.6 Envelope Protein" J. Virol. (October 1998) 72, 10, 8264-8272).

Claims 1, 3, 5, 8-12, 18-20 and 31-34 are interpreted as noted above. Belyakov et al. disclose intrarectally administering a modified vaccinia virus Ankara wherein the virus encodes an HIV-1 antigen. Belyakov et al. disclose administering the virus multiple times (see para. 4, p. 8265). Based on this disclosure, Belyakov et al. anticipate the subject matter of claims 1, 3, 5, 8-12, 18-20 and 31-34.

Claims 1, 2, 5, 8, 11, 12, 18-20 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Kano et al. (Kano, M. "Induction of SIV-Specific Cellular Immune Responses by Using Recombinant Sendai Viral Vector" 7th Conf. Retrov. and Opportun. Inf. (2000)).

Claims 1, 2, 5, 8, 11, 12, 18-20 and 31-33 are interpreted as noted above. Kano et al. disclose the intranasal vaccination of macaques using a recombinant Sendai vector that encodes antigenic Gag protein. The recombinant vector was administered according to a multiple dose schedule which induced a cytotoxic T-cell response. Based on this disclosure, Kano et al. anticipate the subject matter of claims 1, 2, 5, 8, 11, 12, 18-20 and 31-33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over by *Malone et al. (U.S. Pat. No. 6,110,898) ("Malone").*

Malone teaches all the limitations noted above. Malone et al. does not expressly teach a method wherein the gene delivery vehicle comprises elements (i.e. gene constructs) from two or more alhpaviruses. However, this limitation provides that a sequence from the alphavirus gene delivery vehicle, such as a promoter, may be substituted with a sequence from an alphaviruses of a different serotype. Whether the gene delivery vehicle is derived from one or two alphavirus genomes is immaterial since both embodiments would have a similar structure and function. Thus, modifying Malone's gene delivery to include a second alphavirus construct would have been obvious to one of ordinary skill in the art.

Response to Arguments

35 U.S.C. Section 102(e)

Applicants argue Malone et al. does not anticipate claims 1-5, 8-14, 16-20, 29 and 30 because it fails to teach a multiple dose schedule. Applicants note that the specification characterizes a multiple dose schedule as a "prime-boost administration." This argument is not persuasive because Malone et al. teach a multiple dose schedule as claimed, and described in the specification. Column, 17, lines 15 *et seq.* provide that

"priming, booster and maintenance dosing . . . will be suitable for use in the method of the invention." Thus, Applicants' argument that Malone et al. fails to teach a multiple dose schedule is not persuasive.

Applicants argue that Malone et al. teaches away from the invention because Malone et al. induces generalized mucosal immunity by administering a polynucleotide to mucosal inductor sites, while the invention induces humoral and cellular immunity through mucosal administration of a polynucleotide. This argument is not persuasive for two reasons. First, Applicants' argument relies on limitations that are not recited in the claims. That is, the claims do not require a cellular and humoral immune response. The claims generally require "an immune response." Thus, if Malone et al. is limited to teaching a generalized immune response as Applicants suggest, it would still anticipate the claimed invention.

The second reason that Applicants' argument is not persuasive is that Malone et al. teach mucosal administration. For example, the Summary Of The Invention provides that Malone et al.'s antigen-encoding polynucleotide is "for use in genetic immunization via *mucosal administration* . . . ." (Col. 3, lines 54-57).

Based on the foregoing, the rejection of claims 1-5, 8-14, 16-20, 29 and 30 as anticipated by Malone et al. is maintained.

35 U.S.C. Section 103

Applicant argues Malone et al. fail to teach or suggest using a MHC-I or MHC-II sequence for enhancing mucosal immunity. However, a careful reading of Malone et al. reveals this feature is taught at column 4, lines 60 through 67. This text provides that Malone et al.'s gene delivery vehicle may be used as a tolerizing vaccine by separately

administering histocompatibility genes. Malone et al. therefore teach using a MHC-I or MHC-II sequence as claimed.

The remainder of Applicants' arguments are moot because claims 15 and 21 are rejected under new grounds as discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy M. Brown whose telephone number is (571) 272-0773. The examiner can normally be reached on Monday - Friday, 8am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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